In the specification:

Please replace the title currently in the application with the following title:

--COMPOSITIONS AND METHODS FOR PRODUCTION OF SMALL PEPTIDES--

In the Specification:

Please amend the specification as follows:

Amend the paragraph starting at page 54, line 22, as follows:

a'

Figure 4 depicts an alignment of the amino acid sequence of human GLP-1 (7-37), human GLP-1 (7-36) and GLP-1 derived ~~form~~ from the human fibroblast cell line F G39-38.

Amend the paragraph starting at page 57, line 3, as follows:

a²

Nucleotide sequence information for some of the genes encoding small peptides listed above are found in U.S. Patent No.: 5,118,666 (GLP-1 (7-34) and GLP-1 (7-35))~~00~~; U.S. patent No.: 5,120,712 (GLP-1 (7-37)); U.S. patent No.: 5,424,286 (exendin-4); and Takeda et al. (1987) *Prot. Natl. Acad. Sci. USA* 84 (20):7005-7008. In a preferred embodiment, the nucleic acid sequence encoding a small peptide is a synthetic nucleic acid, e.g., a synthetic nucleic acid which encodes a small peptide wherein at least one non-common or less common codon of the peptide has been replaced by a common codon. In other preferred embodiments, about 10, 20, 30, 40, 50 60, 70, 80, 90% or all of the codons encoding the small peptide have been optimized. Methods of modifying a nucleic acid sequence to encode a common codon are described in U.S. Serial Number 09/407,605 ~~506~~, the contents of which is incorporated herein by reference.

Amend the paragraph starting at page 57, line 22, as follows:

a³

A signal sequence is a sequence which directs a peptide having such sequence to a lipid bilayer, e.g., the endoplasmic reticulum (ER). In a preferred embodiment, the signal peptide also assists in transferring the peptide across the bilayer, for example across the lipid bilayer of the ER and into the ER for further processing. A signal sequence should be of sufficient size and hydro-phobicity to direct the peptide for cellular processing. It has been shown that signal sequences from higher eukaryotes and signal sequence should be of sufficient size and hydro-phobicity to direct the peptide for cellular processing. It has been shown that signal sequences from higher eukaryotes and signal sequence from prokaryotic organisms are interchangeable. *See, e.g.,* Gierasch et al. (1989) *Biochemistry* 28:923-930. Thus, a signal sequence can be derived ~~form~~ from any secreted protein.

Amend the paragraph starting at page 58, line 7, as follows:

Preferably, the nucleic acid sequence encoding the signal sequence is from the pre-region of somatostatin. For example, the nucleic acid encoding the pre-region of human somatostatin. For example, the nucleic acid encoding the pre-region of human somatostatin can be used. The signal sequence of human somatostatin spans ~~form~~ from amino acids 1 to 24 of the amino acid sequence of human somatostatin. *See* Shen et al. (1984) *Science* 224(4645):168-171. Nucleotide sequence information is also available for genes encoding somatostatin from several different species. *See* Bruneau et al, (1998) *Peptides* 19(10):1749-1758 9sheep somatostatin); Hoefler et al. (1986) *Nature* 288:137-141 (anglerfish); Funckes et al. (1983) *J. boil. Chem.* 258:8781-8787 (rat somatostatin).

a4

Amend the paragraph starting at page 59, line 13, as follows:

Nucleotide sequence information is available for genes encoding pro-somatostatin ~~form~~ from various species. *See* Shen et al. (1984) *Science* 224(4645):168-171 (human somatostatin); Bruneau et al. (1998) *Peptides* 19 (101)Z:1749-1758 ~~9~~(sheep somatostatin); Hoefler et al. (1986) *nature* 288;137-141 (anglerfish); Funckes et al. (1983) *J. Biol. Chem.* 258:8781-8787 (rat somatostatin).

a5

Amend the paragraph starting at page 59, line 27, as follows:

Preferred sequence variants include pro-region (or functional fragments thereof) whose sequence differ ~~form~~ from the wild-type sequence by one or more conservative amino acid substitutions or by one or more non-conservative amino acid substitution, deletions, or insertions which do not abolish the functional activity of the pro-region of somatostatin. Conservative substitutions typically include the substitution of one amino acid for another with similar characteristics, e.g., substitutions within the following groups: valine, glycine; glycine, alanine; valine, isoleucine, leucine; asperity acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Other conservative substitutions are known. Preferred sequence variants differ ~~form~~ from a wild type pro-region by at least one but not more than 5, 10, 15, 25 or 50 residues.

a6

Amend the paragraph starting at page 60, line 12, as follows:

a7

One can use art to make fragments or variants. These fragments and variants can be tested to determine if they function as a pro-region by introducing the fragment or variant thereof into an expression vector such as those described in Example I and introducing the vector into a cell. Secretion of a peptide or protein ~~form~~ from the cell can be used to determine whether the fragment or variant of the pro-region is functional. *See, e.g.,* Example II below.

Amend the paragraph starting at page 60, line 20, as follows:

A nucleic acid sequence including a nucleic acid encoding a signal sequence, a nucleic acid encoding the pro-region of somatostatin and a nucleic acid encoding a small heterologous peptide can be assembled by various methods. For example, the entire nucleotide sequence of the signal peptide/pro-region/small peptide fusion protein can be synthesized as a series of overlapping oligonucleotides that are then ligated together. In addition, the nucleic acid sequence for the signal peptide, the pro-region, and the small peptide, may be amplified by PCR

a8

~~form~~ from any starting material that contains the target sequences. PCR primers can be designed to incorporate an endoprotease cleavage site between the pro-region of a somatostatin and the sequence encoding the small heterologous peptide. The fragments can then be joined by overlapping PCR. The nucleic sequence may also be assembled by traditional cloning techniques. This method would involve, for example, the isolation of a signal peptide, the pro-region of somatostatin and a small peptide-encoding nucleotide sequence by restriction digest, followed by ligation of the fragments to an oligonucleotide encoding a site, e.g., a cleavage site, e.g., an endoprotease cleavage site.

~~Amend the paragraph starting at page 61, line 6, as follows:~~

Primary and secondary cells to be genetically engineered can be obtained ~~form~~ from a variety of tissues and include cell types which can be maintained propagated in culture. For

a9

example, primary and secondary cells include fibroblasts, keratinocytes, epithelial cells (e.g., mammary epithelial cells, intestinal epithelial cells), endothelial cells, glial cells, neural cells, formed elements of the blood (e.g., lymphocytes, bone marrow cells), muscle cells (myoblasts)

and precursors of these somatic cell types. Primary cells are preferably obtained from the individual to whom the genetically engineered primary or secondary cells are administered. However, primary cells may be obtained for a donor (other than the recipient) of the same species or another species (e.g., mouse, rat, rabbit, cat, dog, pig, cow, bird, sheep, goat, horse).

a9

Amend the paragraph starting at page 62, line 30, as follows:

The resulting primary cell mixture can be transfected directly or it can be cultured first, removed ~~form~~ from the culture plate a resuspended before transfection is carries out. Primary cells or secondary cells are combined with exogenous nucleic acid sequence to e.g., stably integrated into their genomes and, optionally, DNA encoding a selectable marker, and treated in order to accomplish transfection. The exogenous nucleic acid sequence and selectable marker-encoding DNA can either be on separate constructs or on a single construct. An appropriate quantity of DNA is used to ensure that at least one stably transfected cell containing and appropriately expressing exogenous DNA is produced. In general, approximately 0.1 to 500 μg of DNA is used.

a10

Amend the paragraph starting at page 65, line 3, as follows:

The patient has a small skin biopsy performed; this is a simple procedure which can be performed on an outpatient basis. The piece of skin, approximately the size of a matched, is taken, for example, ~~form~~ from under the arm and requires about one minute to remove. The sample is processed, resulting in isolation of the patient's cell (in case, fibroblasts) and genetically engineered to produce the GLP-1. Based on the age, weight, and clinical condition of the patient, the required number of cells are grown in large-scale culture. The entire process should require 4-6 weeks and, at the end of that time, the appropriate number of genetically engineered cells are introduced into the individual, once again as an outpatient (e.g., by injecting them back under the patient's skin). The patient is now capable of producing GLP-1 which ameliorates one or more symptoms of diabetes.

a11

Amend the paragraph starting at page 65, line 17, as follows:

a12

As this example suggests, the cells used will generally be patient-specific genetically engineered cells. It is possible, however, to obtain cells ~~form~~ from another individual of the same species or form a different species. Use of such cells might require administration of an immunosuppressant, alteration of histocompatibility antigens, or use of a barrier device to prevent rejection of the implanted cells.

Amend the paragraph starting at page 66, line 4, as follows:

a13

Another agent with can be used to inhibit T cell activity in a subject is an antibody, or fragment of derivative thereof. Antibodies capable of depleting or sequestering T cells *in vivo* are known in the art. Polyclonal antisera can be used, for example, anti-lymphocyte serum. Alternatively, one or more monoclonal antibodies can be used. Preferred T cell depleting antibodies include monoclonal antibodies which bind to CD2, CD3, CD4, CD8, CD40, CD40, ligand on the cell surface. Such antibodies are known in the art and are commercially available, for example, ~~form~~ from American Type Culture Collection. A preferred antibody for binding CD3 on human T cells is OKT3 (ATCC CRL 8001).

Amend the paragraph starting at page 68, line 18, as follows:

a14

To construct pXIT-28, amino acids through 37 and the stop codon of GLP-1 were amplified ~~form~~ from the pXIT-1 template by PCR using Taq polymerase. The PCR was done with the following oligonucleotides:

Amend the paragraph starting at page 72, line 16, as follows:

a15

The sequence was found to be identical to human GLP-1(7-36) as shown in Figure 4, Figure 4 shows the alignment of human GLP-1 (7-37), human GLP-1 (7-36), and GLP-1 derived ~~form~~ from the human fibroblast cell line FG39-38 (HF GLP-1). Sequence identity between human GLP-1 (7-36) and human fibroblast GLP-1 is 100%. The Arg 30 of human GLP-1 (7-36) is amidated. The micro sequencer used to sequence human fibroblast GLP-1 did not distinguish normal Arg from amidated Arg. The presence or absence of an amide group will be determined by mass spectrometry. No residue was detected after Arg 30 of HF GLP-1 in this sample.

However, radioimmunoassay data indicates that both the 7-37 and 7-36 peptides are secreted by human fibroblasts transfected with pXIT-39.